

**The significance of sentinel lymph node micrometastasis in breast cancer:
comparing outcomes with and without axillary clearance**

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Abstract

Background: Management of micrometastasis in the sentinel node is a controversial topic. Most of the guidelines don't recommend further axillary treatment if micrometastasis are the only finding in the sentinel node. However, some evidence suggests that micrometastasis have significant effect on long term outcomes and therefore indicate systemic treatment.

Method: Retrospective cohort study reviewing the management of patients with micrometastasis in the sentinel nodes. Two groups were compared, those who had further axillary clearance and those who had not. The primary endpoints were loco-regional recurrence and lymphoedema rate. The secondary endpoints were distant metastasis rate, OS and DFS.

Results: 95 patients were found to have micrometastasis or ITC in the axillary SNB over a period of 10 years. Of those, 38 patients had axillary clearance after SNB, while 57 did not. Lymphedema rate was 18.4% in the axillary clearance group versus 0% in the no axillary clearance group ($p < 0.001$). The LRR event was rare therefore not compared. Distant metastasis rate was 7.01% in the SNB group versus 2.6% in the axillary clearance group.

There were no mortalities in the axillary clearance group. This compares to 7.01% among the patients who didn't have axillary clearance. All the patients who died had developed distant metastasis as a cause of death. There was a difference in OS between the two groups in favor of the axillary clearance group ($p = 0.004$).

Discussion: Although not an indication for axillary clearance recent guidelines, micrometastasis and ITC found in the SNB are a sign of a biologically different disease. This important information should be taken in consideration when planning the adjuvant treatment in those patients among other factors considered.

Keywords

Micrometastasis Axilla Survival Clearance

Introduction

The further management of micrometastatic disease in the era of axillary sentinel node biopsy (SNB) has been evolving. Gradually, guidelines are shifting away from clearing the axilla if micrometastasis are found during sentinel node biopsy [1] [2] [3].

The Association of Breast Surgery of England (ABS) consensus statement in 2014 on the management of the axilla reflected this [4]. The recent IBCSG 23-01 trial showed no difference in outcome in terms of disease free survival (DFS) or overall survival (OS) when axillary treatment was omitted for micrometastasis in SNB [5]. However, the earlier MIRROR study showed that patients with micrometastasis and isolated tumour cells (ITC) who didn't receive systemic treatment had a higher event rate than those who did [6]. This suggests that micrometastases are a sign of a systemic disease, which needs to be considered when planning treatment for those patients.

This is retrospective cohort study of breast cancer patients with sentinel node micrometastases. The aim of the study was to detect any difference in outcomes in patients with micrometastases in the sentinel node with and without axillary clearance. We compared two groups of patients from this cohort, those who had a subsequent axillary clearance and those who did not. The primary endpoints for comparison were loco-regional recurrence (LRR) and lymphedema. The secondary endpoints were distant metastasis rate, overall survival (OS) and disease-free survival (DFS).

Micrometastasis are defined as metastatic disease in the axilla which is smaller than 2.0 mm but larger than 0.2 mm. Isolated Tumour Cells (ITC) are defined as metastatic disease smaller

than or equal to 0.2 mm according to the American Joint Committee on Cancer (AJCC) staging manual [7].

Lymphoedema was defined as clinically evident swelling of the arm on the treated side, with referral to the lymphedema service. Loco-regional recurrence is defined as any tumour developing in the ipsilateral breast and/or the axilla after the primary treatment. Distant metastasis are define as any tumour metastasis developing in distal organs after completion of primary treatment.

Patients and Methods

This study was conducted at the Royal Devon and Exeter Hospital, treating more than 600 new breast cancer patients per year. We looked at all breast cancer patients who were diagnosed with micrometastasis in the axilla over a 10 years' period (2006 to 2015). This cohort of patients was divided into 2 groups based on their subsequent management following the detection of SNB micrometastases: those who had a completion axillary clearance, and those who did not. Pathological characteristics of the primary tumour were recorded and accounted for in the statistical analysis. This included the histological subtype of the tumour (ductal, lobular and others); size and grade of the tumour; ER/PR and HER2 receptor status.

All patients had their treatment plan including adjuvant treatment considered and documented at the multidisciplinary team (MDT) meeting.

Clinical follow-up was by physical examination 6 monthly for 2 years and annually thereafter up to 5 years with annual mammography for 5 years.

The outcomes for the two groups were compared. The primary endpoints were LRR and lymphoedema rate and the secondary endpoints were distant metastasis rate, OS and DFS.

Patients were excluded from the study if they had received neoadjuvant chemotherapy treatment, since this may have altered the tumour biology and confound the results.

Radiotherapy schedules and boost fields were documented and considered in the multivariate analysis.

Data were analyzed using IBM SPSS advanced statistics version 22 (SPSS Inc., Chicago, IL).

Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test or Fisher's exact test were used to examine the relation between qualitative variables. For non-normally distributed data, comparison between two groups was done using Mann-Whitney test (non-parametric t-test). Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test. All tests were two-tailed. A p-value < 0.05 was considered significant.

Results

From 2006 to 2015, 95 patients were found to have micrometastasis or ITC in the axillary SNB. Of those, 38 patients had axillary clearance following SNB, while 57 did not.

The tumor characteristics, size of micrometastasis and adjuvant treatment within the two groups are summarized in Table 1. The median follow-up duration was 34.2 months. Two patients left from Exeter after a short follow-up period and were therefore not included in the survival analysis. Six patients had received neoadjuvant chemotherapy and were excluded.

54 patients (56.84%) were treated with wide local excision, while 41 (43.15%) had a mastectomy.

There was a statistically significant difference in the rates of lymphoedema between the two groups. Lymphedema rate was 18.4% (7 patients) in the axillary clearance group versus 0% (0 patients) in the no axillary clearance group (Chi Square test, $p < 0.001$).

There was no detectable difference in the loco-regional recurrence rate between the two groups. The LRR event was rare. Only one patient in the no axillary clearance patients group developed local recurrence during the period of the study. This axillary recurrence was detected after 5 years from the initial treatment.

Four patients of the 57 who had SNB only (7.01%) developed distant metastasis during the follow-up period of the study. While only one patient of the 38 in axillary clearance group (2.6%) developed distant metastasis.

There were no deaths during the period of follow-up within the axillary clearance group. This compared to 7.01% among SNB only cohort. The distant metastasis in this cohort developed at 1, 3, 4 and 5 years following initial treatment. All the patients who died had already developed distant metastasis. Three of the four patients died within the same year of the diagnosis of distant metastasis, while one patient died 3 years later.

The cumulative 5 years OS of all patients with micrometastatic disease was 84.7%.

There was a statistically significant difference when DFS survival analysis was done using Kaplan-Meier curve between the two groups. The difference was 40% in favor of the axillary clearance group (Mantle-Cox test, $p = 0.004$). This is shown in Figure 1.

There was similar difference in DFS between the two groups, although this was not statistically significant ($p = 0.1$). Figure 2.

On multivariate analysis of OS between the two groups, axillary clearance remained the only significant factor accounting for the statistical difference. Analysis included size of micrometastasis ($p = 0.664$), size of the tumor ($p = 0.981$), grade of the tumor ($p = 0.2$), adjuvant radiotherapy ($p = 0.418$), adjuvant chemotherapy ($p = 0.747$) and adjuvant Herceptin ($p = 0.567$). However, endocrine treatment showed a difference but this did not quite reach significance, with a p value of 0.054. Table 1.

Of the 57 the patients within the SNB only group, 10 patients had the axilla included in the field of radiotherapy. All 10 were treated during the last 5 years. None of these patients developed lymphoedema, in contrast with those who had axillary clearance ($p = 0.013$).

Among the axillary clearance group, 11 patients had axillary clearance upfront without SNB for various reasons. The only finding in the axillary nodes however was micrometastasis or ITC. Those patients were included within the axillary clearance following SNB group as they have same natural history.

In the 28 patients who had axillary clearance following SNB, three patients had further positive axillary lymph nodes (10.7%). None of which had more than two further nodes containing metastases. All the further positive nodes contained micrometastatic disease.

Discussion

This study addresses the question of whether axillary clearance can be safely omitted when micrometastasis or ITC are found in the sentinel node. This remains a controversial issue as data from different studies are being published [8] [9].

In our study, axillary clearance did not add much staging information when it was performed following micrometastasis in SNB. Only 10% of patients had further axillary disease and none had more than 2 further positive lymph nodes. The rate of lymphedema was significantly higher in patients who had axillary clearance, this is in concordance of the established evidence available [10].

There was a 7% difference in mortality between the two groups. Of those patients, 50% have not received any adjuvant systemic treatment. It is fair to say that micrometastasis detected in the SNB indicate a systemic disease not only an axillary localized disease. In this aspect, our study results correlate with the MIRROR trial results where the micrometastasis were found to be a sign of a different systemic disease that needs to be considered in the algorithm of adjuvant treatment planning [11].

There was a statistically significant difference in the cumulative OS and DFS between the two groups of patients in this study which was in favor of axillary clearance. However, there was also statistically significant effect on OS noticed with endocrine treatment in ER positive patients and also with patients where radiotherapy field was extended to tangentially include the axilla. This result correlates with the ACOSG Z-001 study results where all patients reportedly received some form of radiotherapy to the axilla by modifying the field [12].

Lymphedema was higher in patients who had axillary clearance compared to those who had axillary radiotherapy. This result is concordant with the recent AMAROS trial published data [13].

We recognize many limitations to our study. Primarily, this is a retrospective cohort study over 10 year's duration. During those 10 years, the treatment of the axilla has markedly changed. This is reflected in our study by the fact that most of the patients who didn't receive further axillary clearance for micrometastasis were the more recent patients in the study. The

number of patients in the study could be a limitation too, but is comparable to other retrospective studies who tried to address the topic [14] [15] [16]. The median follow-up period of the study is also short. The molecular classification of the tumour was not included as a prognostic factor in this study.

However, the main limitation of our study is the small number of events in both groups. This particularly affects the survival analysis and makes accounting to different factors in the analysis not statistically significant. Therefore, data and conclusions should be taken with caution.

The data regarding the axilla inclusion in radiotherapy field should be taken with caution. The number of patients with those criteria is very small despite the statistical significance of the results.

Although not an indication for axillary clearance in most of the recent guidelines, micrometastasis and ITC found in the SNB seem to affect the survival of the patients.

This important information should be taken in consideration when planning the adjuvant treatment in those patients among other factors considered.

On the basis of current evidence axillary clearance could probably be safely omitted after SNB when micrometastasis or ITC are found given the higher rate of lymphedema and the little staging information it further adds [17]. But, on making this decision, the field of radiotherapy and the adjuvant systemic treatment need to be considered. This is concordant with the ABS consensus statement which takes in consideration in the algorithm of further axillary treatment many factors. Namely the type of surgical treatment (mastectomy versus breast conserving) and therefore the radiotherapy and its field and also the ER receptor status and therefore endocrine treatment [4].

Our discussion is that although micrometastatic disease in the axilla doesn't dictate further axillary surgery, it is an indication of a biologically different systemic disease. This needs to be taken in consideration when planning adjuvant systemic treatment in those patients as it clearly affects their survival-

Currently, there are not enough data to support the use of more aggressive systemic therapies when ITC and micrometastases are found in the sentinel node. The data from different studies are controversial.

However, the question of the impact micrometastasis have on the OS of the patients remains to be addressed. Further prospective study of long-term follow-up of patients is required, with design of high quality randomized studies desirable.

Table 1. Characteristics of the two groups of patients

| | SNB | ANC | P value |
|-----------------------------------|------------|------------|----------------|
| Total number | 57 (100%) | 38 (100%) | |
| Number of Micrometastases | | | |
| ITC | 3 (5.2%) | 4 (10.5%) | |
| 1 | 48 (83.2%) | 31 (81.5%) | |
| 2 | 6 (10.5%) | 3 (7.8%) | |
| Median Size of Micrometastases | 0.73 mm | 0.63 mm | |
| Median Number of Nodes at the SNB | 2.9 | 1.74 | |
| Tumour Type | | | |
| IDC | 51 (89.4%) | 30 (78.9%) | 0.158 |
| ILC | 5 (8.7%) | 6 (15.7%) | |
| Other | 1 (1.7%) | 2 (5.2%) | |
| Tumour Size | | | 0.500 |
| <20 mm | 34 (59.6%) | 20 (52.6%) | |
| >20 mm | 23 (40.3%) | 18 (47.3%) | |
| Tumour Grade | | | |
| 1 | 10 (17.5%) | 3 (7.8%) | 0.439 |
| 2 | 33 (57.8%) | 25 (65.7%) | |
| 3 | 12 (21%) | 10 (26.3%) | |
| Not available | 2 (3.5%) | | |
| Surgery | | | |
| Mastectomy | 19 (33.3%) | 22 (57.8%) | |
| WLE | 38 (66.6%) | 16 (42.1%) | |
| Adjuvant Treatment | | | |
| Chemotherapy | 16 (28%) | 17 (44.7%) | 0.095 |
| Herceptin | 4 (7%) | 4 (10.5%) | 0.727 |
| Radiotherapy | 49 (85.9%) | 30 (78.9%) | 0.371 |
| Endocrine Treatment | 48 (84.2%) | 35 (92.1%) | 0.256 |
| Loco-Regional Recurrence | 1 (1.7%) | 0 (0%) | 0.419 |
| Distant Metastasis | 4 (7%) | 1 (2.6%) | 0.346 |
| Lymphedema | 0 (0%) | 7 (18.4%) | <0.001 |
| Mortality | 4 (7%) | 0 (0%) | 0.048 |

Figure 1. Overall Survival between the two groups

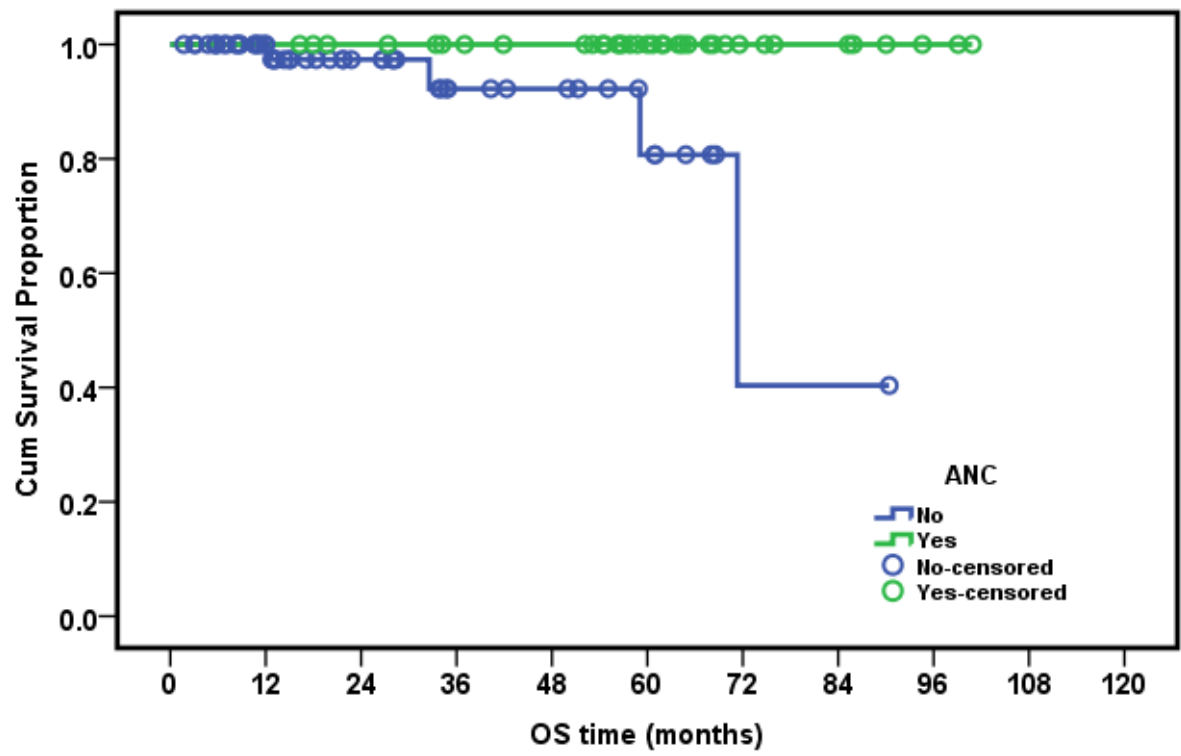
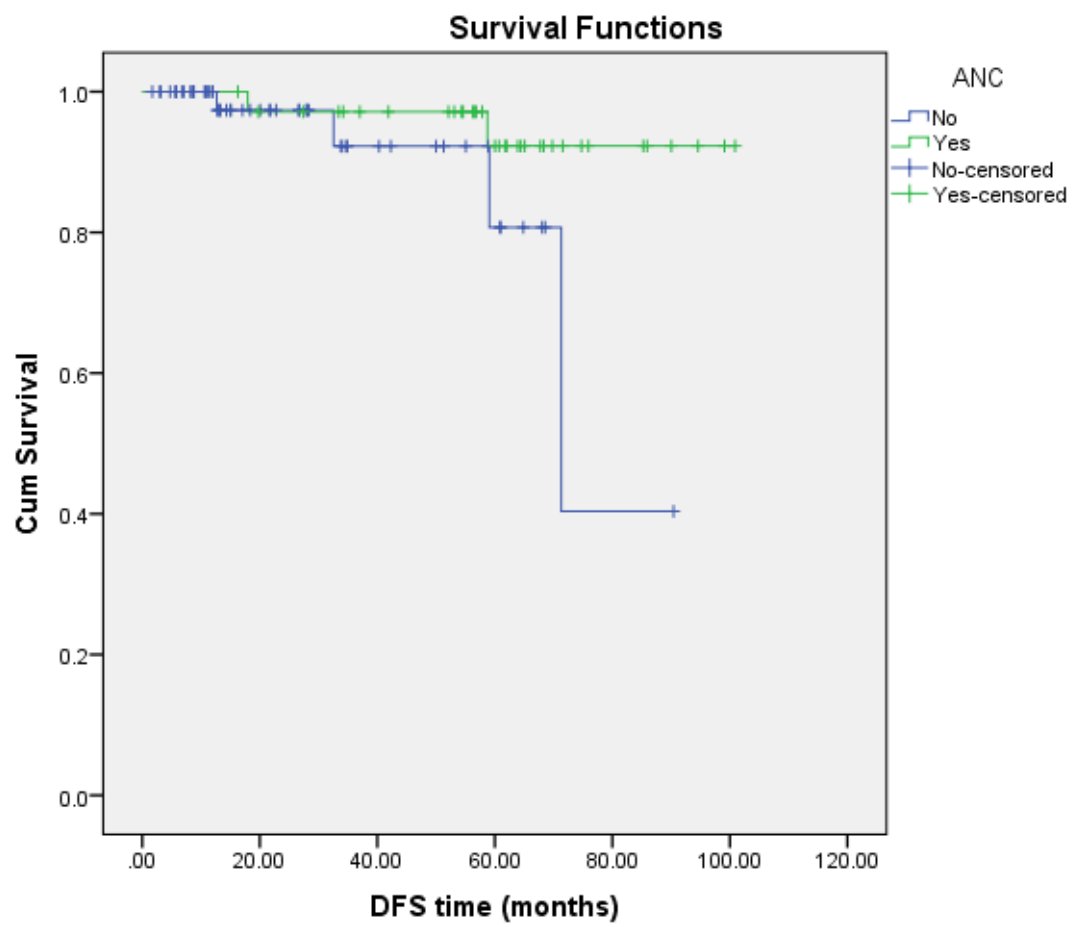


Figure 2. Disease Free Survival between the two groups



Conflict of Interest Statement

Authors declare there is no conflict of interest in this article.

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Ethical Approval

Ethical approval was not required for this study.

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